IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Stephen J. Russell et al. Art Unit : 1648
Serial No. : 09/668,196 Examiner : Zachariah Lucas
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Title : METHOD FOR LIMITING THE GROWTH OF CANCER CELLS USING AN ATTENUATED MEASLES VIRUS

MAIL STOP APPEAL BRIEF - PATENT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

BRIEF ON APPEAL

(1) Real Party in Interest

The real party in interest is Mayo Foundation for Medical Education and Research.

(2) Related Appeals and Interferences

None.

(3) Status of Claims

Claims 8, 10, 23, 25, and 27 have been previously cancelled without prejudice.

Claims 1-7, 9, 11-22, 24, 26, and 28-33 are pending and stand finally rejected.

(4) Status of Amendments

All amendments have been entered.

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(5) Summary of Invention

The invention relates to administering attenuated measles virus to a mammal under conditions wherein the number of viable cancer cells in the mammal is reduced. *See, e.g.*, the section of Applicants' specification extending from page 2, line 15 to page 3, line 24.

(6) Issues

(1) Whether Applicants' specification enables the subject matter of claims 31 and 32?

(2) Whether the subject matter of claims 1-7, 9, 11-17, 20-22, 24, and 28-33 would have been obvious in view of the Bateman *et al.* 2000 reference (Bateman *et al.*, *Cancer Research*, 60:1492-1497 (2000)) combined with the Weibel *et al.* reference (Weibel *et al.*, *Arch. Dis. Childhood*, 48:532-536 (1973)), the Lindarkis *et al.* abstract (Lindarkis *et al.*, *Gene Therapy*, 6, Suppl. 1:S4, Abstract 13 (1999)), the Bateman *et al.* 1999 abstract (Bateman *et al.*, *Gene Therapy*, 6, Suppl. 1:S6, Abstract 24 (1999)), the Taqi *et al.* reference (Taqi *et al.*, *Lancet*, May 16, p. 1112 (1981)), the Bluming *et al.* reference (Bluming *et al.*, *Lancet*, July 10, pp. 105-106 (1971)) and the Johnston *et al.* reference (*J. Virol.*, 73(8):6903-6915))?

(3) Whether the subject matter of claims 1-7, 9, 11-22, 24, 26, and 28-33 would have been obvious in view of the Bateman *et al.* 2000 reference combined with the Usonis *et al.* reference (Usonis *et al.*, *Ped. Inf. Dis. J.*, 18:42-48 (1999)), the Lindarkis *et al.* abstract (Lindarkis *et al.*, *Gene Therapy*, 6, Suppl. 1:S4, Abstract 13 (1999)), the Bateman *et al.* 1999 abstract (Bateman *et al.*, *Gene Therapy*, 6, Suppl. 1:S6, Abstract 24 (1999)), the Taqi *et al.* reference (Taqi *et al.*, *Lancet*, May 16, p. 1112 (1981)), the Bluming *et al.* reference (Bluming *et al.*, *Lancet*, July 10, pp. 105-106 (1971)) and the Johnston *et al.* reference (*J. Virol.*, 73(8):6903-6915))?

(4) Whether the subject matter of claims 16 and 17 would have been obvious in view of the Bateman *et al.* reference (*Cancer Research*, 60:1492-1497, 2000) combined with either the Weibel *et al.* reference (Weibel *et al.*, *Arch. Dis. Childhood*, 48:532-536 (1973)) or the Usonis *et al.* reference (Usonis *et al.*, *Ped. Inf. Dis. J.*, 18:42-48 (1999)), in further view of the Asada reference (*Cancer*, 34:1907-1928 (1974)) or the Sato reference (*Int. J. Oral Surg.*, 8:205-211 (1979)) and further in light of the Lindarkis *et al.* abstract (Lindarkis *et al.*, *Gene Therapy*, 6, Suppl. 1:S4, Abstract 13 (1999)), the Bateman *et al.* 1999 abstract (Bateman *et al.*, *Gene*

Therapy, 6, Suppl. 1:S6, Abstract 24 (1999)), the Taqi *et al.* reference (Taqi *et al.*, *Lancet*, May 16, p. 1112 (1981)), the Bluming *et al.* reference (Bluming *et al.*, *Lancet*, July 10, pp. 105-106 (1971)), and the Johnston *et al.* reference (*J. Virol.*, 73(8):6903-6915))?

(5) Whether the subject matter of claims 18 and 19 would have been obvious in view of the Bateman *et al.* reference (*Cancer Research*, 60:1492-1497, 2000) combined with either the Weibel *et al.* reference (Weibel *et al.*, *Arch. Dis. Childhood*, 48:532-536 (1973)) or the Usonis *et al.* reference (Usonis *et al.*, *Ped. Inf. Dis. J.*, 18:42-48 (1999)), in view of the Duprex *et al.* reference (Duprex *et al.*, *J. Virol.*, 73:9568-9575 (1999)), and further in light of the Lindarkis *et al.* abstract (Lindarkis *et al.*, *Gene Therapy*, 6, Suppl. 1:S4, Abstract 13 (1999)), the Bateman *et al.* 1999 abstract (Bateman *et al.*, *Gene Therapy*, 6, Suppl. 1:S6, Abstract 24 (1999)), the Taqi *et al.* reference (Taqi *et al.*, *Lancet*, May 16, p. 1112 (1981)), the Bluming *et al.* reference (Bluming *et al.*, *Lancet*, July 10, pp. 105-106 (1971)), and the Johnston *et al.* reference (*J. Virol.*, 73(8):6903-6915))?

(6) Whether the subject matter of claim 20 would have been obvious in view of the Galanis *et al.* abstract (Galanis *et al.*, *Gene Therapy*, 6, Suppl. 1:S7, Abstract 28 (1999)) or the Russell *et al.* abstract (Russell *et al.*, *Proc. Am. Assoc. Cancer Res.*, 41:259, Abstract 1648 (2000)) combined with either the Weibel *et al.* reference (Weibel *et al.*, *Arch. Dis. Childhood*, 48:532-536 (1973)) or the Usonis *et al.* reference (Usonis *et al.*, *Ped. Inf. Dis. J.*, 18:42-48 (1999)), in view of the Lindarkis *et al.* abstract (Lindarkis *et al.*, *Gene Therapy*, 6, Suppl. 1:S4, Abstract 13 (1999)), the Bateman *et al.* 1999 abstract (Bateman *et al.*, *Gene Therapy*, 6, Suppl. 1:S6, Abstract 24 (1999)), the Taqi *et al.* reference (Taqi *et al.*, *Lancet*, May 16, p. 1112 (1981)), the Bluming *et al.* reference (Bluming *et al.*, *Lancet*, July 10, pp. 105-106 (1971)), and the Johnston *et al.* reference (*J. Virol.*, 73(8):6903-6915))?

(7) Grouping of Claims

For Issue #1, claims 31 and 32 stand or fall together.

For the remaining issues, claims 1, 5, 9, 24, 28, 29, and 30 stand or fall together. Claims 2-4, 6, 7, 11-22, 26, and 31-33 are separately patentable and fall into separately patentable groups as follows. Claims 2-4 stand or fall together. Claim 6 stands or falls alone. Claim 7 stands or falls alone. Claim 11 stands or falls alone. Claim 12 stands or falls alone. Claim 13

stands or falls alone. Claim 14 stands or falls alone. Claim 15 stands or falls alone. Claim 16 stands or falls alone. Claim 17 stands or falls alone. Claims 18 and 19 stand or fall together. Claim 20 stands or falls alone. Claim 21 stands or falls alone. Claim 22 stands or falls alone. Claim 26 stands or falls alone. Claim 31 stands or falls alone. Claim 32 stands or falls alone. Claim 33 stands or falls alone.

(8) Argument

Issue #1: Whether Applicants' specification enables the subject matter of claims 31 and 32?

A. Grouping of Claims for Issue #1

Claims 31 and 32 stand or fall together.

B. Arguments for Reversal of Examiner's Rejection Regarding Issue #1

Claim 31 recites that the attenuated virus comprises at least one point mutation in a wild-type or attenuated measles virus genome. Claim 32, which depends from claim 31, recites that the attenuated virus does not comprise contiguous point mutations. A person having ordinary skill in the art at the time Applicants filed would have been able to obtain an attenuated measles virus containing point mutations. For example, a person having ordinary skill in the art at the time Applicants filed would have been able to use routine techniques to mutate an attenuated measles virus and test the resulting mutated measles virus to confirm that it is attenuated. In addition, standard molecular biology techniques such as site directed mutagenesis can be used to introduce point mutations into an attenuated measles virus. In fact, a person having ordinary skill in the art would have been able to use site directed mutagenesis to introduce multiple noncontiguous point mutations into an attenuated measles virus. Thus, no undue experimentation is needed for a person having ordinary skill in the art to practice the presently claimed invention.

In light of the above, Applicants respectfully request reversal of the Examiner's rejection of claims 31 and 32 under 35 U.S.C. § 112, first paragraph.

Issue #2: Whether the subject matter of claims 1-7, 9, 11-17, 20-22, 24, and 28-33 would have been obvious in view of the Bateman *et al.* 2000 reference combined with the Weibel *et al.* reference, Lindarkis *et al.* abstract, the Bateman *et al.* 1999 abstract, the Taqi *et al.* reference, the Bluming *et al.* reference, and the Johnston *et al.* reference?

A. Grouping of Claims for Issue #2

Of the claims rejected in light of the seven cited references, claims 1, 5, 9, 24, and 28-30 stand or fall together. The remaining rejected claims, claims 2-4, 6, 7, 11-17, 20-22, and 31-33, fall into separately patentable groups as follows. Claims 2-4 stand or fall together, and form a separately patentable group since any teaching or suggestion that a person having ordinary skill in the art should administer attenuated measles virus to a mammal to reduce the number of viable cancer cells does not necessarily anticipate or render obvious a claim reciting directly administering attenuated measles virus to a cancer cell or tumor.

Claim 6 stands or falls alone as a separately patentable claim since any teaching or suggestion that a person having ordinary skill in the art should administer attenuated measles virus to a mammal to reduce the number of viable cancer cells does not necessarily anticipate or render obvious a claim reciting continuously providing an attenuated measles virus formulation to the mammal.

Claim 7 stands or falls alone as a separately patentable claim since any teaching or suggestion that a person having ordinary skill in the art should administer attenuated measles virus to a mammal to reduce the number of viable cancer cells does not necessarily anticipate or render obvious a claim reciting providing an attenuated measles virus formulation to the mammal in pulses.

Claim 11 stands or falls alone as a separately patentable claim since any teaching or suggestion that a person having ordinary skill in the art should administer attenuated measles virus to a mammal to reduce the number of viable cancer cells does not necessarily anticipate or render obvious a claim reciting administering the attenuated measles virus at a dose greater than about 10^3 pfus.

Claim 12 stands or falls alone as a separately patentable claim since any teaching or suggestion that a person having ordinary skill in the art should administer attenuated measles virus to a mammal to reduce the number of viable cancer cells does not necessarily anticipate or render obvious a claim reciting administering the attenuated measles virus at a dose of about 10^5 pfus.

Claim 13 stands or falls alone as a separately patentable claim since any teaching or suggestion that a person having ordinary skill in the art should administer attenuated measles virus to a mammal to reduce the number of viable cancer cells does not necessarily anticipate or render obvious a claim reciting administering the attenuated measles virus at a dose of about 10^6 pfus.

Claim 14 stands or falls alone as a separately patentable claim since any teaching or suggestion that a person having ordinary skill in the art should administer attenuated measles virus to a mammal to reduce the number of viable cancer cells does not necessarily anticipate or render obvious a claim reciting administering the attenuated measles virus at a dose of about 10^7 pfus.

Claim 15 stands or falls alone as a separately patentable claim since any teaching or suggestion that a person having ordinary skill in the art should administer attenuated measles virus to a mammal to reduce the number of viable cancer cells does not necessarily anticipate or render obvious a claim reciting administering the attenuated measles virus at a dose of about 10^8 pfus.

Claim 16 stands or falls alone as a separately patentable claim since any teaching or suggestion that a person having ordinary skill in the art should administer attenuated measles virus to a mammal to reduce the number of viable cancer cells does not necessarily anticipate or render obvious a claim reciting administering the attenuated measles virus in a composition containing attenuated mumps virus and attenuated rubella virus.

Claim 17 stands or falls alone as a separately patentable claim since any teaching or suggestion that a person having ordinary skill in the art should administer attenuated measles virus to a mammal to reduce the number of viable cancer cells does not necessarily anticipate or render obvious a claim reciting administering the attenuated measles virus in a composition containing attenuated rubella virus.

Claim 20 stands or falls alone as a separately patentable claim since any teaching or suggestion that a person having ordinary skill in the art should administer attenuated measles virus to a mammal to reduce the number of viable cancer cells does not necessarily anticipate or render obvious a claim reciting a reduction in the number of melanoma cells, carcinoma cells, glioma cells, or myeloma cells.

Claim 21 stands or falls alone as a separately patentable claim since any teaching or suggestion that a person having ordinary skill in the art should administer attenuated measles virus to a mammal to reduce the number of viable cancer cells does not necessarily anticipate or render obvious a claim reciting a reduction in the number of myeloma cells.

Claim 22 stands or falls alone as a separately patentable claim since any teaching or suggestion that a person having ordinary skill in the art should administer attenuated measles virus to a mammal to reduce the number of viable cancer cells does not necessarily anticipate or render obvious a claim reciting a reduction in the number of Non-Hodgkin's lymphoma cells.

Claim 31 stands or falls alone as a separately patentable claim since any teaching or suggestion that a person having ordinary skill in the art should administer attenuated measles virus to a mammal to reduce the number of viable cancer cells does not necessarily anticipate or render obvious a claim reciting that the attenuated measles virus contains at least one point mutation.

Claim 32 stands or falls alone as a separately patentable claim since any teaching or suggestion that a person having ordinary skill in the art should administer attenuated measles virus to a mammal to reduce the number of viable cancer cells does not necessarily anticipate or render obvious a claim reciting that the attenuated measles virus contains at least one point mutation and not contiguous point mutations.

Claim 33 stands or falls alone as a separately patentable claim since any teaching or suggestion that a person having ordinary skill in the art should administer attenuated measles virus to a mammal to reduce the number of viable cancer cells does not necessarily anticipate or render obvious a claim reciting administering the attenuated measles virus at a dose of about 10^{12} pfu.

B. Arguments for Reversal of Examiner's Rejection Regarding Issue #2

Proper analysis under 35 U.S.C. § 103 requires consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should carry out the claimed process, and (2) whether the prior art would also have revealed that in so carrying out, those of ordinary skill would have a reasonable expectation of success. *See, In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). It is axiomatic that in order to establish a *prima facie* case of obviousness under 35 U.S.C. § 103, a prior art reference must teach or suggest, alone or in combination with other prior art references, each and every element of the claimed invention. *See, e.g.*, MPEP § 2143. The Federal Circuit warns that "both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure," and that "it is impermissible to use the claimed invention as a 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious." *See, In re Dow Chemical Co.*, 837 F.2d 469 (Fed. Cir. 1988) and *In re Fritch*, 972 F.2d 1260 (Fed Cir. 1992).

In addition, the so-called "secondary" considerations, such as unexpected results and long-felt but unmet need, should be considered in every case when present. See, e.g., *In re Sernaker*, 702 F.2d 989 (Fed. Cir. 1983) citing *In re Fielder and Underwood*, 471 F.2d 640 (Cust. & Pat. App. 1973). In fact, the Federal Circuit stated that:

> evidence of secondary considerations may often be the most probative and cogent evidence in the record. It may often establish that an invention appearing to have been obvious in light of the prior art was not. It is to be considered as part of all the evidence, not just when the decisionmaker remains in doubt after reviewing the art.

Stratoflex, Inc., v. Aeroquip Corp., 713 F.2d 1530, 1538-39 (Fed. Cir. 1983).

1. Claims 1, 5, 9, 24, and 28-30

In the Official Action mailed January 14, 2003, the Examiner stated the "main difference between the claimed invention and the prior art is that the claimed invention uses attenuated measles virus as a vector rather than the plasmids used in the Bateman article." The Examiner also stated that the "plasmids used in the reference were just a convenient vector." To support this allegation, the Examiner stated that this "was highlighted by the teachings of both Lindarkis and the Bateman abstract, which suggest the use of viral vectors to introduce the DNA into

cells." Then, the Examiner concluded that "it would be obvious to one of ordinary skill in the art to use the attenuated measles virus taught by Weibel as a convenient vector for the measles virus DNA."

Applicants respectfully disagree. First, the claimed invention is very different from the prior art. Claims 1, 5, 9, 24, and 28-30, which stand or fall together, recite a method for reducing the number of viable cancer cells by administering an attenuated measles virus to the mammal. The Bateman 2000 reference discloses the effects of transiently transfecting cultured cells with plasmid DNA encoding fusogenic membrane glycoproteins (FMGs) and the effects of vaccinating mice with tumor cells transfected with plasmid DNA encoding FMGs. Killing cells in a dish and treating animals with transfected tumor cells are vastly different from administering an attenuated measles virus to a mammal to reduce the number of viable cancer cells. The Bateman 2000 reference also discloses that established tumors can be eradicated by transduction with plasmid DNA encoding FMG cDNA. *See*, page 1496. This experiment, however, was performed using a different protocol as reported in a correction published in the same journal on September 1, 2000. *See*, page 4978. Instead of transfecting established tumors *in vivo* and assessing tumor growth, tumor cells were transfected and then implanted 24 hours later to assess their ability to grow tumors. In fact, according to the published correction, the heading on page 1496 was corrected to read as follows: "Tumorigenicity Can Be Abrogated by Pretransduction with Plasmid DNA Encoding FMG cDNA" and not "Established Tumors Can Be Eradicated by Transduction with Plasmid DNA Encoding FMG cDNA." A copy of this published correction is attached following the Appendix of Claims.

Second, none of the seven cited references, either alone or in combination, teaches or suggests using an attenuated measles virus as a convenient vector to deliver measles virus DNA, let alone to reduce the number of viable cancer cells in a mammal. Again, the Bateman *et al.* 2000 reference is a research article that discloses the effects of transfecting tissue culture cells *in vitro* and the effects of transplanting transfected tissue culture cells into animals. It is noted that page 1496 of the Bateman 2000 reference discloses that ongoing experiments demonstrate that a lentiviral vector was capable of eradicating established tumors. This falls far short of suggesting that a person having ordinary skill in the art should use an attenuated measles virus to reduce the number of viable cancer cells in a mammal. In addition, it is unclear from the Bateman 2000

reference how such a lentiviral vector was used to eradicate an established tumor since the Bateman 2000 reference fails to disclose, for example, the genetic identity of the lentiviral vector, the manner in which the lentiviral vector was made and used, and the type of tumor eradicated.

The Johnston *et al.* reference discloses that wild-type, lymphotropic measles viruses possess different cell tropisms than vaccine strains of measles virus. In addition, the Johnston *et al.* reference discloses using recombinant vaccine measles viruses to determine that wild-type envelope glycoproteins affect cell entry and cell-to-cell spread in adherent cell cultures. At no point does the Johnston *et al.* reference teach or suggest using an attenuated measles virus to reduce the number of viable cancer cells in a mammal.

The Weibel *et al.* reference is a 1973 publication that discloses vaccination results obtained from children vaccinated with a combined measles and mumps vaccine. The Weibel *et al.* reference has nothing to do with viral vectors, the use of viral vectors, or the use of attenuated measles virus to reduce the number of cancer cells in a mammal. In fact, at no point does the Weibel *et al.* reference disclose that an attenuated measles virus would be a convenient vector to deliver measles virus DNA. Applicants see no reason why a person having ordinary skill in the art would have looked to this vaccine art for teachings related to tumor eradication. The Linardakis *et al.* abstract discloses developing plasmid- and viral-vectors expressing FMGs under the control of inducible promoters. The Bateman *et al.* 1999 abstract discloses that the authors are constructing retroviral and adenoviral vectors for *in vivo* delivery to tumors. Clearly, developing viral vectors expressing FMGs under the control of inducible promoters and constructing retroviral and adenoviral vectors are unrelated to the use of an attenuated measles virus to reduce the number of viable cancer cells in a mammal. In addition, at no point does the Linardakis *et al.* abstract or the Bateman *et al.* 1999 abstract disclose that an attenuated measles virus would be a convenient vector to deliver measles virus DNA. The Taqi *et al.* reference is a 1981 report of the unexplained regression of Hodgkin's disease after measles infection in a 7-year-old girl. Likewise, the Bluming *et al.* reference is a 1971 report of the unexplained regression of Burkitt's lymphoma in association with measles infection. Neither of these two reports discusses viral vectors or the use of viral vectors. In fact, at no point do these two reports disclose that an attenuated measles virus would be a convenient vector to deliver measles virus

DNA. It is noted that the authors of the Taqi reference proposed "a trial of attenuated live measles vaccine as in adjuvant to chemotherapy in the treatment of Hodgkin's disease in children." It is unclear from this reference what the authors are proposing. The phrase "in adjuvant to chemotherapy" is not clear. Nevertheless, proposing a trial to study the possibility of using attenuated measles vaccine in some manner falls far short of suggesting that a person having ordinary skill in the art should carry out the claimed invention. In fact, a person having ordinary skill in the art at the time Applicants filed reading the unexplained associations and the 1981 proposed trial would not have been motivated, with the required reasonable expectation of success, to use an attenuated measles virus to reduce the number of cancer cells in a mammal. Thus, taken together, it is clear that a person having ordinary skill in the art at the time Applicants filed reading the cited references would not have been motivated to administer an attenuated measles virus to a mammal to reduce the number of viable cancer cells in that mammal.

The combination of cited references fails to provide any information indicating that an attenuated measles virus can be administered to a mammal to reduce the number of viable cancer cells in the mammal. In fact, a person having ordinary skill in that art at the time Applicants filed, reading the cited references would not have had any information regarding the ability of an attenuated measles virus (e.g., a nonpathogenic measles virus) to reduce the number of viable cancer cells in a mammal. It is noted that the unexplained associations reported in the Taqi *et al.* reference and the Bluming *et al.* reference were with respect to measles infections, not administration of an attenuated measles virus. Having a measles infection is quite different from receiving an attenuated measles virus such as a measles virus vaccine. In fact, measles infections typically cause rash, high fever, cough, runny nose, and red, watery eyes with complications including diarrhea, ear infections, pneumonia, encephalitis, seizures, and death. Administration of an attenuated measles virus such as a measles virus vaccine does not typically cause these symptoms or complications. In fact, according to the Weibel *et al.* reference, the Moraten line measles vaccine may cause mild febrile reactions, rash, and generalized malaise in a portion of recipients. *See*, page 534. Since the cited references fail to provide the required reasonable expectation of success in achieving reduction in the number of viable cancer cells in a mammal by administering an attenuated measles virus, the presently claimed invention is not obvious.

Even assuming for the sake of argument that the Examiner established a proper *prima facie* case of obviousness, the presently claimed invention is nevertheless not obvious as evidenced by Applicants' surprising results supporting the claimed invention. At the time Applicants filed, a person having ordinary skilled in that art would have understood that reducing the number of viable cancer cells in a mammal is generally an unpredictable process. Thus, Applicants' findings regarding attenuated measles viruses and cancer cell viability within a mammal are important and unexpected results. Specifically, Applicants' originally filed specification discloses the surprising findings that attenuated measles virus, when administered to a mammal, prevents tumor growth (*See, e.g.*, page 22), decreases the rate of tumor progression (*See, e.g.*, page 23 and Figures 2B and C), and causes tumor regression (*See, e.g.*, page 23 and Figure 2A). The unexpected nature of these findings highlights the non-obviousness of the presently claimed invention.

Additional evidence supporting the patentability of the presently claimed invention is the fact that the claimed invention satisfies a long-felt need that was recognized, persistent, and not solved by others. It is well established that the long-felt need is measured from the date the problem is identified, not the date of the most pertinent prior art references. *See, e.g.*, MPEP § 716.04 and *Texas Instruments Inc. v. Int'l Trade Comm'n*, 988 F.2d 1165, 1179 (Fed. Cir. 1993).

Having the ability to reduce the number of cancer cells within a mammal is a need that has existed for many years. For example, the Stenbeck *et al.* reference (*ACTA Oncologica*, 34:881-891 (1995)) discloses three decades of data relating to cancer survival. Thus, it is clear that cancer kills many people and effective cancer treatments are needed. This need has persisted through the years and continued to exist at the time of Applicants' invention as evidenced by the Cancer Statistics for 2000 published by the American Cancer Society. *See*, Greenlee *et al.*, *CA Cancer J. Clin.*, 50:7-33 (2000).

Applicants' presently claimed invention fulfills this long-felt need. For example, claim 1 recites a method for reducing the number of viable cancer cells in a mammal by administering attenuated measles virus to the mammal. Applicants' specification provides multiple working examples demonstrating the effective treatment of cancer. In fact, Applicants' specification discloses the successful use of attenuated measles viruses to prevent tumor growth, decrease the rate of tumor progression, and cause tumor regression. Thus, a person having ordinary skill in

the art reading Applicants' specification would have understood that Applicants' invention provides an effective method for reducing the number of viable cancer cells in a mammal. This evidence supports the fact that the presently claimed invention is not obvious.

In light of the above, Applicants respectfully request reversal of the Examiner's rejection of claims 1, 5, 9, 24, and 28-30 under 35 U.S.C. § 103.

2. Claim 6

None of the cited reference, either alone or in combination, teaches or suggests using an attenuated measles virus to reduce the number of cancer cells in a mammal by continuously providing an attenuated measles virus formulation to the mammal. In fact, the Weibel *et al.* reference, which is the only cited reference that discloses administering a measles virus vaccine to a mammal, discloses subcutaneously administering the vaccine. At no point does this reference, or any other cited reference, disclose continuously providing an attenuated measles virus formulation to the mammal, let alone continuously providing an attenuated measles virus formulation to the mammal to reduce the number of cancer cells in a mammal.

In light of the above, Applicants respectfully request reversal of the Examiner's rejection of claim 6 under 35 U.S.C. § 103.

3. Claim 7

None of the cited reference, either alone or in combination, teaches or suggests using an attenuated measles virus to reduce the number of cancer cells in a mammal by providing an attenuated measles virus formulation to the mammal in pulses. Again, the Weibel *et al.* reference, which is the only cited reference that discloses administering a measles virus vaccine to a mammal, discloses subcutaneously administering the vaccine. At no point does this reference, or any other cited reference, disclose providing an attenuated measles virus formulation to the mammal in pulses, let alone providing an attenuated measles virus formulation to the mammal in pulses to reduce the number of cancer cells in a mammal.

In light of the above, Applicants respectfully request reversal of the Examiner's rejection of claim 7 under 35 U.S.C. § 103.

4. Claim 11

None of the cited reference, either alone or in combination, teaches or suggests using an attenuated measles virus at a dose greater than about 10^3 pfus to reduce the number of cancer cells in a mammal. In fact, the combination of cited references fails to suggest using a single dose of attenuated measles virus to reduce the number of cancer cells in a mammal.

In light of the above, Applicants respectfully request reversal of the Examiner's rejection of claim 11 under 35 U.S.C. § 103.

5. Claim 12

None of the cited reference, either alone or in combination, teaches or suggests using an attenuated measles virus at a dose of about 10^5 pfus to reduce the number of cancer cells in a mammal. In fact, the combination of cited references fails to suggest using a single dose of attenuated measles virus to reduce the number of cancer cells in a mammal.

In light of the above, Applicants respectfully request reversal of the Examiner's rejection of claim 12 under 35 U.S.C. § 103.

6. Claim 13

None of the cited reference, either alone or in combination, teaches or suggests using an attenuated measles virus at a dose of about 10^6 pfus to reduce the number of cancer cells in a mammal. In fact, the combination of cited references fails to suggest using a single dose of attenuated measles virus to reduce the number of cancer cells in a mammal.

In light of the above, Applicants respectfully request reversal of the Examiner's rejection of claim 13 under 35 U.S.C. § 103.

7. Claim 14

None of the cited reference, either alone or in combination, teaches or suggests using an attenuated measles virus at a dose of about 10^7 pfus to reduce the number of cancer cells in a mammal. In fact, the combination of cited references fails to suggest using a single dose of attenuated measles virus to reduce the number of cancer cells in a mammal.

In light of the above, Applicants respectfully request reversal of the Examiner's rejection of claim 14 under 35 U.S.C. § 103.

8. Claim 15

None of the cited reference, either alone or in combination, teaches or suggests using an attenuated measles virus at a dose of about 10^8 pfus to reduce the number of cancer cells in a mammal. In fact, the combination of cited references fails to suggest using a single dose of attenuated measles virus to reduce the number of cancer cells in a mammal.

In light of the above, Applicants respectfully request reversal of the Examiner's rejection of claim 15 under 35 U.S.C. § 103.

9. Claim 16

None of the cited reference, either alone or in combination, teaches or suggests using an attenuated measles virus in a composition containing attenuated mumps virus and attenuated rubella virus to reduce the number of cancer cells in a mammal. In fact, the combination of cited references fails to suggest using any combination of attenuated viruses to reduce the number of cancer cells in a mammal.

In light of the above, Applicants respectfully request reversal of the Examiner's rejection of claim 16 under 35 U.S.C. § 103.

10. Claim 17

None of the cited reference, either alone or in combination, teaches or suggests using an attenuated measles virus in a composition containing attenuated rubella virus to reduce the number of cancer cells in a mammal. In fact, the combination of cited references fails to suggest using any combination of attenuated viruses to reduce the number of cancer cells in a mammal.

In light of the above, Applicants respectfully request reversal of the Examiner's rejection of claim 17 under 35 U.S.C. § 103.

11. Claim 20

None of the cited reference, either alone or in combination, teaches or suggests using an attenuated measles virus to reduce the number of melanoma cells, carcinoma cells, glioma cells, or myeloma cells in a mammal. In fact, the combination of cited references fails to suggest using an attenuated measles virus to reduce the number of any cancer cell in a mammal, let alone the number of melanoma cells, carcinoma cells, glioma cells, or myeloma cells in a mammal.

In light of the above, Applicants respectfully request reversal of the Examiner's rejection of claim 20 under 35 U.S.C. § 103.

12. Claim 21

None of the cited reference, either alone or in combination, teaches or suggests using an attenuated measles virus to reduce the number of myeloma cells in a mammal. In fact, the combination of cited references fails to suggest using an attenuated measles virus to reduce the number of any cancer cell in a mammal, let alone the number of myeloma cells in a mammal.

In light of the above, Applicants respectfully request reversal of the Examiner's rejection of claim 21 under 35 U.S.C. § 103.

13. Claim 22

None of the cited reference, either alone or in combination, teaches or suggests using an attenuated measles virus to reduce the number of Non-Hodgkin's lymphoma cells in a mammal. In fact, the combination of cited references fails to suggest using an attenuated measles virus to reduce the number of any cancer cell in a mammal, let alone the number of Non-Hodgkin's lymphoma cells in a mammal.

In light of the above, Applicants respectfully request reversal of the Examiner's rejection of claim 22 under 35 U.S.C. § 103.

14. Claim 31

None of the cited reference, either alone or in combination, teaches or suggests using an attenuated measles virus to reduce the number of cancer cells in a mammal where the attenuated measles virus contains at least one point mutation. In fact, the combination of cited references

fails to suggest reducing the number of cancer cells in a mammal using any type of attenuated measles virus containing a point mutation.

In light of the above, Applicants respectfully request reversal of the Examiner's rejection of claim 31 under 35 U.S.C. § 103.

15. Claim 32

None of the cited reference, either alone or in combination, teaches or suggests using an attenuated measles virus to reduce the number of cancer cells in a mammal where the attenuated measles virus contains at least one point mutation and not contiguous point mutations. In fact, the combination of cited references fails to suggest reducing the number of cancer cells in a mammal using any type of attenuated measles virus containing a point mutation and not contiguous point mutations.

In light of the above, Applicants respectfully request reversal of the Examiner's rejection of claim 32 under 35 U.S.C. § 103.

16. Claim 33

None of the cited reference, either alone or in combination, teaches or suggests using an attenuated measles virus at a dose of about 10^{12} pfus to reduce the number of cancer cells in a mammal. In fact, the combination of cited references fails to suggest using a single dose of attenuated measles virus to reduce the number of cancer cells in a mammal.

In light of the above, Applicants respectfully request reversal of the Examiner's rejection of claim 33 under 35 U.S.C. § 103.

Issue #3: Whether the subject matter of claims 1-7, 9, 11-22, 24, 26, and 28-33 would have been obvious in view of the Bateman *et al.* 2000 reference combined with the Usonis *et al.* reference, the Lindarkis *et al.* abstract, the Bateman *et al.* 1999 abstract, the Taqi *et al.* reference, the Bluming *et al.* reference, and the Johnston *et al.* reference?

A. Grouping of Claims for Issue #3

Of the claims rejected in light of these seven references, claims 1, 5, 9, 24, and 28-30 stand or fall together. Claims 2-4, 6, 7, 11-22, and 31-33 fall into separately patentable groups as set forth above under the Grouping of Claims for Issue #2. Claim 26 stands or falls alone as a separately patentable claim since any teaching or suggestion that a person having ordinary skill in the art should administer attenuated measles virus to a mammal to reduce the number of viable cancer cells does not necessarily anticipate or render obvious a claim reciting that the attenuated measles virus is provided within an MMR-II vaccine.

B. Arguments for Reversal of Examiner's Rejection Regarding Issue #3

Again, proper analysis under 35 U.S.C. § 103 requires consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should carry out the claimed process, and (2) whether the prior art would also have revealed that in so carrying out, those of ordinary skill would have a reasonable expectation of success. *See, In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). It is axiomatic that in order to establish a *prima facie* case of obviousness under 35 U.S.C. § 103, a prior art reference must teach or suggest, alone or in combination with other prior art references, each and every element of the claimed invention. *See, e.g.*, MPEP § 2143. The Federal Circuit warns that "both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure," and that "it is impermissible to use the claimed invention as a 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious." *See, In re Dow Chemical Co.*, 837 F.2d 469 (Fed. Cir. 1988) and *In re Fritch*, 972 F.2d 1260 (Fed Cir. 1992).

In addition, the so-called "secondary" considerations, such as unexpected results and long-felt but unmet need, should be considered in every case when present. *See, e.g., In re*

Sernaker, 702 F.2d 989 (Fed. Cir. 1983) citing *In re Fielder and Underwood*, 471 F.2d 640 (Cust. & Pat. App. 1973). In fact, the Federal Circuit stated that:

> evidence of secondary considerations may often be the most probative and cogent evidence in the record. It may often establish that an invention appearing to have been obvious in light of the prior art was not. It is to be considered as part of all the evidence, not just when the decisionmaker remains in doubt after reviewing the art.

Stratoflex, Inc., v. Aeroquip Corp., 713 F.2d 1530, 1538-39 (Fed. Cir. 1983).

1. Claims 1, 5, 9, 24, and 28-30

As explained above, the claimed invention is very different from the prior art. Claims 1, 5, 9, 24, and 28-30, which stand or fall together, recite a method for reducing the number of viable cancer cells by administering an attenuated measles virus to the mammal. The Bateman 2000 reference discloses the effects of transiently transfecting cultured cells with plasmid DNA encoding fusogenic membrane glycoproteins (FMGs) and the effects of vaccinating mice with tumor cells transfected with plasmid DNA encoding FMGs. Killing cells in a dish and treating animals with transfected tumor cells is vastly different from administering an attenuated measles virus to a mammal to reduce the number of viable cancer cells. The Bateman 2000 reference also discloses that established tumors can be eradicated by transduction with plasmid DNA encoding FMG cDNA. *See*, page 1496. This experiment, however, was performed using a different protocol as reported in a correction published in the same journal on September 1, 2000. Instead of transfecting established tumors *in vivo* and assessing tumor growth, tumor cells were transfected and then implanted 24 hours later to assess their ability to grow tumors. In fact, according to the published correction, the heading on page 1496 should read as follows: "Tumorigenicity Can Be Abrogated by Pretransduction with Plasmid DNA Encoding FMG cDNA." A copy of this published correction is attached as Appendix 2.

None of the seven cited references, either alone or in combination, teaches or suggests using an attenuated measles virus as a convenient vector to deliver measles virus DNA, let alone to reduce the number of viable cancer cells in a mammal. Again, the Bateman *et al.* 2000 reference is a research article that discloses the effects of transfecting tissue culture cells *in vitro* and the effects of transplanting transfected tissue culture cells into animals. It is noted that page

1496 of the Bateman 2000 reference discloses that ongoing experiments demonstrate that a lentiviral vector was capable of eradicating established tumors. This falls far short of suggesting that a person having ordinary skill in the art should use an attenuated measles virus to reduce the number of viable cancer cells in a mammal. In addition, it is unclear from the Bateman 2000 reference how such a lentiviral vector was used to eradicate an established tumor since the Bateman 2000 reference fails to disclose, for example, the genetic identity of the lentiviral vector, the manner in which the lentiviral vector was made and used, and the type of tumor eradicated.

The Johnston *et al.* reference discloses that wild-type, lymphotropic measles viruses possess different cell tropisms than vaccine strains of measles virus. In addition, the Johnston *et al.* reference discloses using recombinant vaccine measles viruses to determine that wild-type envelope glycoproteins affect cell entry and cell-to-cell spread in adherent cell cultures. At no point does the Johnston *et al.* reference teach or suggest using an attenuated measles virus to reduce the number of viable cancer cells in a mammal.

The Usonis *et al.* reference, like the Weibel *et al.* reference discussed above, discloses vaccination results obtained from children vaccinated with a combined vaccine. In this case, the combined vaccine was a measles, mumps, and rubella vaccine. The Usonis *et al.* reference has nothing to do with viral vectors, the use of viral vectors, or the use of attenuated measles virus to reduce the number of viable cancer cells in a mammal. Applicants see no reason why a person having ordinary skill in the art would have looked to this vaccine art for teachings related to tumor eradication. The Linardakis *et al.* abstract discloses developing plasmid- and viral-vectors expressing FMGs under the control of inducible promoters. The Bateman *et al.* 1999 abstract discloses that the authors are constructing retroviral and adenoviral vectors for *in vivo* delivery to tumors. Clearly, developing viral vectors expressing FMGs under the control of inducible promoters and constructing retroviral and adenoviral vectors are unrelated to the use of an attenuated measles virus to reduce the number of viable cancer cells in a mammal. In addition, at no point does the Linardakis *et al.* abstract or the Bateman *et al.* 1999 abstract disclose that an attenuated measles virus would be a convenient vector to deliver measles virus DNA. The Taqi *et al.* reference is a 1981 report of the unexplained regression of Hodgkin's disease after measles infection in a 7-year-old girl. Likewise, the Bluming *et al.* reference is a 1971 report of the

unexplained regression of Burkitt's lymphoma in association with measles infection. Neither of these two reports discusses viral vectors or the use of viral vectors. In fact, at no point do these two reports disclose that an attenuated measles virus would be a convenient vector to deliver measles virus DNA. It is noted that the authors of the Taqi reference proposed "a trial of attenuated live measles vaccine as in adjuvant to chemotherapy in the treatment of Hodgkin's disease in children." It is unclear from this reference what the authors are proposing. The phrase "in adjuvant to chemotherapy" is not clear. Nevertheless, proposing a trial to study the possibility of using attenuated measles vaccine in some manner falls far short of suggesting that a person having ordinary skill in the art should carry out the claimed invention. In fact, a person having ordinary skill in the art at the time Applicants filed reading the unexplained associations and the 1981 proposed trial would not have been motivated, with the required reasonable expectation of success, to use an attenuated measles virus to reduce the number of cancer cells in a mammal. Thus, taken together, it is clear that a person having ordinary skill in the art at the time Applicants filed reading the cited references would not have been motivated to administer an attenuated measles virus to a mammal to reduce the number of viable cancer cells in that mammal.

Moreover, the combination of cited references fails to provide any information indicating that an attenuated measles virus can be administered to a mammal to reduce the number of viable cancer cells in the mammal. In fact, a person having ordinary skill in that art at the time Applicants filed, reading the cited references would not have had any information regarding the ability of an attenuated measles virus (e.g., a nonpathogenic measles virus) to reduce the number of viable cancer cells in a mammal. Since the cited references fail to provide the required reasonable expectation of success in achieving reduction in the number of viable cancer cells in a mammal by administering an attenuated measles virus, the presently claimed invention is not obvious.

Even assuming for the sake of argument that the Examiner established a proper *prima facie* case of obviousness, the presently claimed invention is nevertheless not obvious as evidenced by Applicants' surprising results supporting the claimed invention. At the time Applicants filed, a person having ordinary skilled in that art would have understood that reducing the number of viable cancer cells in a mammal is generally an unpredictable process. Thus,

Applicants' findings regarding attenuated measles viruses and cancer cell viability within a mammal are important and unexpected results. Specifically, Applicants' originally filed specification discloses the surprising findings that attenuated measles virus, when administered to a mammal, prevents tumor growth (*See, e.g.*, page 22), decreases the rate of tumor progression (*See, e.g.*, page 23 and Figures 2B and C), and causes tumor regression (*See, e.g.*, page 23 and Figure 2A). The unexpected nature of these findings highlights the non-obviousness of the presently claimed invention.

Additional evidence supporting the patentability of the presently claimed invention is the fact that the claimed invention satisfies a long-felt need that was recognized, persistent, and not solved by others. It is well established that the long-felt need is measured from the date the problem is identified, not the date of the most pertinent prior art references. *See, e.g.*, MPEP § 716.04 and *Texas Instruments Inc. v. Int'l Trade Comm'n*, 988 F.2d 1165, 1179 (Fed. Cir. 1993).

Having the ability to reduce the number of cancer cells within a mammal is a need that has existed for quite some time. For example, the Stenbeck *et al.* reference (*ACTA Oncologica*, 34:881-891 (1995)) discloses three decades of data relating to cancer survival. Thus, it is clear that cancer kills many people and effective cancer treatments are needed. This need has persisted through the years and continued to exist at the time of Applicants' invention as evidenced by the Cancer Statistics for 2000 published by the American Cancer Society. *See*, Greenlee *et al.*, *CA Cancer J. Clin.*, 50:7-33 (2000).

Applicants' presently claimed invention fulfills this long-felt need. For example, claim 1 recites a method for reducing the number of viable cancer cells in a mammal by administering attenuated measles virus to the mammal. Applicants' specification provides multiple working examples demonstrating the effective treatment of cancer. In fact, Applicants' specification discloses the successful use of attenuated measles viruses to prevent tumor growth, decrease the rate of tumor progression, and cause tumor regression. Thus, a person having ordinary skill in the art reading Applicants' specification would have understood that Applicants' invention provides an effective method for reducing the number of viable cancer cells in a mammal. This evidence supports the fact that the presently claimed invention is not obvious.

In light of the above, Applicants respectfully request reversal of the Examiner's rejection of claims 1, 5, 9, 24, and 28-30 under 35 U.S.C. § 103.

2. Claim 6

None of the seven cited references, either alone or in combination, teaches or suggests using an attenuated measles virus to reduce the number of cancer cells in a mammal by continuously providing an attenuated measles virus formulation to the mammal. In fact, the Usonis *et al.* reference, which discloses administering a measles virus vaccine to children, discloses subcutaneously administering the vaccine. At no point does this reference, or the other cited references, disclose continuously providing an attenuated measles virus formulation to the mammal, let alone continuously providing an attenuated measles virus formulation to the mammal to reduce the number of cancer cells in a mammal.

In light of the above, Applicants respectfully request reversal of the Examiner's rejection of claim 6 under 35 U.S.C. § 103.

3. Claim 7

None of the seven cited references, either alone or in combination, teaches or suggests using an attenuated measles virus to reduce the number of cancer cells in a mammal by providing an attenuated measles virus formulation to the mammal in pulses. Again, the Usonis *et al.* reference, which discloses administering a measles virus vaccine to children, discloses subcutaneously administering the vaccine. At no point does this reference, or the other cited references, disclose providing an attenuated measles virus formulation to the mammal in pulses, let alone providing an attenuated measles virus formulation to the mammal in pulses to reduce the number of cancer cells in a mammal.

In light of the above, Applicants respectfully request reversal of the Examiner's rejection of claim 7 under 35 U.S.C. § 103.

4. Claim 11

None of the seven cited references, either alone or in combination, teaches or suggests using an attenuated measles virus at a dose greater than about 10^3 pfus to reduce the number of cancer cells in a mammal. In fact, the combination of cited references fails to suggest using a single dose of attenuated measles virus to reduce the number of cancer cells in a mammal.

In light of the above, Applicants respectfully request reversal of the Examiner's rejection of claim 11 under 35 U.S.C. § 103.

5. Claim 12

None of the seven cited references, either alone or in combination, teaches or suggests using an attenuated measles virus at a dose of about 10^5 pfus to reduce the number of cancer cells in a mammal. In fact, the combination of cited references fails to suggest using a single dose of attenuated measles virus to reduce the number of cancer cells in a mammal.

In light of the above, Applicants respectfully request reversal of the Examiner's rejection of claim 12 under 35 U.S.C. § 103.

6. Claim 13

None of the seven cited references, either alone or in combination, teaches or suggests using an attenuated measles virus at a dose of about 10^6 pfus to reduce the number of cancer cells in a mammal. In fact, the combination of cited references fails to suggest using a single dose of attenuated measles virus to reduce the number of cancer cells in a mammal.

In light of the above, Applicants respectfully request reversal of the Examiner's rejection of claim 13 under 35 U.S.C. § 103.

7. Claim 14

None of the seven cited references, either alone or in combination, teaches or suggests using an attenuated measles virus at a dose of about 10^7 pfus to reduce the number of cancer cells in a mammal. In fact, the combination of cited references fails to suggest using a single dose of attenuated measles virus to reduce the number of cancer cells in a mammal.

In light of the above, Applicants respectfully request reversal of the Examiner's rejection of claim 14 under 35 U.S.C. § 103.

8. Claim 15

None of the seven cited references, either alone or in combination, teaches or suggests using an attenuated measles virus at a dose of about 10^8 pfus to reduce the number of cancer cells

in a mammal. In fact, the combination of cited references fails to suggest using a single dose of attenuated measles virus to reduce the number of cancer cells in a mammal.

In light of the above, Applicants respectfully request reversal of the Examiner's rejection of claim 15 under 35 U.S.C. § 103.

9. Claim 16

None of the seven cited references, either alone or in combination, teaches or suggests using an attenuated measles virus in a composition containing attenuated mumps virus and attenuated rubella virus to reduce the number of cancer cells in a mammal. In fact, the combination of cited references fails to suggest using any combination of attenuated viruses to reduce the number of cancer cells in a mammal.

In light of the above, Applicants respectfully request reversal of the Examiner's rejection of claim 16 under 35 U.S.C. § 103.

10. Claim 17

None of the seven cited references, either alone or in combination, teaches or suggests using an attenuated measles virus in a composition containing attenuated rubella virus to reduce the number of cancer cells in a mammal. In fact, the combination of cited references fails to suggest using any combination of attenuated viruses to reduce the number of cancer cells in a mammal.

In light of the above, Applicants respectfully request reversal of the Examiner's rejection of claim 17 under 35 U.S.C. § 103.

11. Claims 18 and 19

None of the seven cited references, either alone or in combination, teaches or suggests using an attenuated measles virus to reduce the number of cancer cells in a mammal where the attenuated measles virus is genetically modified to express a marker polypeptide such β-galactosidase or green fluorescent protein. In fact, the combination of cited references fails to suggest using any type of genetically modified attenuated measles viruses to reduce the number of cancer cells in a mammal.

In light of the above, Applicants respectfully request reversal of the Examiner's rejection of claims 18 and 19 under 35 U.S.C. § 103.

12. Claim 20

None of the seven cited references, either alone or in combination, teaches or suggests using an attenuated measles virus to reduce the number of melanoma cells, carcinoma cells, glioma cells, or myeloma cells in a mammal. In fact, the combination of cited references fails to suggest using an attenuated measles virus to reduce the number of any cancer cell in a mammal, let alone the number of melanoma cells, carcinoma cells, glioma cells, or myeloma cells in a mammal.

In light of the above, Applicants respectfully request reversal of the Examiner's rejection of claim 20 under 35 U.S.C. § 103.

13. Claim 21

None of the seven cited references, either alone or in combination, teaches or suggests using an attenuated measles virus to reduce the number of myeloma cells in a mammal. In fact, the combination of cited references fails to suggest using an attenuated measles virus to reduce the number of any cancer cell in a mammal, let alone the number of myeloma cells in a mammal.

In light of the above, Applicants respectfully request reversal of the Examiner's rejection of claim 21 under 35 U.S.C. § 103.

14. Claim 22

None of the seven cited references, either alone or in combination, teaches or suggests using an attenuated measles virus to reduce the number of Non-Hodgkin's lymphoma cells in a mammal. In fact, the combination of cited references fails to suggest using an attenuated measles virus to reduce the number of any cancer cell in a mammal, let alone the number of Non-Hodgkin's lymphoma cells in a mammal.

In light of the above, Applicants respectfully request reversal of the Examiner's rejection of claim 22 under 35 U.S.C. § 103.

15. Claim 26

None of the seven cited references, either alone or in combination, teaches or suggests using an attenuated measles virus provided within an MMR-II vaccine to reduce the number of viable cancer cells in a mammal. In fact, the combination of cited references fails to suggest using any type of attenuated measles virus vaccine to reduce the number of viable cancer cell in a mammal.

In light of the above, Applicants respectfully request reversal of the Examiner's rejection of claim 26 under 35 U.S.C. § 103.

16. Claim 31

None of the seven cited references, either alone or in combination, teaches or suggests using an attenuated measles virus to reduce the number of cancer cells in a mammal where the attenuated measles virus contains at least one point mutation. In fact, the combination of cited references fails to suggest reducing the number of cancer cells in a mammal using any type of attenuated measles virus containing a point mutation.

In light of the above, Applicants respectfully request reversal of the Examiner's rejection of claim 31 under 35 U.S.C. § 103.

17. Claim 32

None of the seven cited references, either alone or in combination, teaches or suggests using an attenuated measles virus to reduce the number of cancer cells in a mammal where the attenuated measles virus contains at least one point mutation and not contiguous point mutations. In fact, the combination of cited references fails to suggest reducing the number of cancer cells in a mammal using any type of attenuated measles virus containing a point mutation and not contiguous point mutations.

In light of the above, Applicants respectfully request reversal of the Examiner's rejection of claim 32 under 35 U.S.C. § 103.

18. Claim 33

None of the seven cited references, either alone or in combination, teaches or suggests using an attenuated measles virus at a dose of about 10^{12} pfus to reduce the number of cancer cells in a mammal. In fact, the combination of cited references fails to suggest using a single dose of attenuated measles virus to reduce the number of cancer cells in a mammal.

In light of the above, Applicants respectfully request reversal of the Examiner's rejection of claim 33 under 35 U.S.C. § 103.

Issue #4: Whether the subject matter of claims 16 and 17 would have been obvious in view of the Bateman *et al.* 2000 reference combined with either the Weibel *et al.* reference or the Usonis *et al.* reference, in further view of the Asada reference or the Sato reference, and further in light of the Lindarkis *et al.* abstract, the Bateman *et al.* 1999 abstract, the Taqi *et al.* reference, the Bluming *et al.* reference, and the Johnston *et al.* reference?

A. Grouping of Claims for Issue #4

Claims 16 and 17 are separately patentable.

B. Arguments for Reversal of Examiner's Rejection Regarding Issue #4

1. Claim 16

Claim 16 recites a method for reducing the number of viable cancer cells in a mammal using an attenuated measles virus in a composition containing attenuated mumps virus and attenuated rubella virus. The combination of cited references does not teach or suggest such a method. For the same reasons explained above, the combination of (1) the Bateman *et al.* 2000 reference, (2) the Weibel *et al.* reference, (3) the Usonis *et al.* reference, (4) the Lindarkis *et al.* abstract, (5) the Bateman *et al.* 1999 abstract, (6) the Taqi *et al.* reference, (7) the Bluming *et al.* reference, and (8) the Johnston *et al.* reference does not teach or suggest reducing the number of viable cancer cells in a mammal using an attenuated measles virus. Moreover, at no point does the combination of these eight references teach or suggest using an attenuated measles virus in a composition containing attenuated mumps virus and attenuated rubella virus to reduce the

number of viable cancer cells in a mammal. The Asada reference and the Sato *et al.* reference fail to correct the deficiencies of these eight references. The Asada reference discloses treating human cancer with mumps virus, while the Sato *et al.* reference discloses an attenuated mumps virus therapy of carcinoma of the maxillary sinus. Neither of these two references, when combined with the other eight references, provides any teaching or suggestion to use an attenuated measles virus in a composition containing attenuated mumps virus and attenuated rubella virus to reduce the number of viable cancer cells in a mammal. Thus, the combination of the ten cited references does not render claim 16 obvious.

In light of the above, Applicants respectfully request reversal of the Examiner's rejection of claim 16 under 35 U.S.C. § 103.

2. Claim 17

Claim 17 recites a method for reducing the number of viable cancer cells in a mammal using an attenuated measles virus in a composition containing attenuated rubella virus. The combination of cited references does not teach or suggest such a method. For the reasons explained above, the combination of (1) the Bateman *et al.* 2000 reference, (2) the Weibel *et al.* reference, (3) the Usonis *et al.* reference, (4) the Lindarkis *et al.* abstract, (5) the Bateman *et al.* 1999 abstract, (6) the Taqi *et al.* reference, (7) the Bluming *et al.* reference, and (8) the Johnston *et al.* reference does not teach or suggest reducing the number of viable cancer cells in a mammal using an attenuated measles virus. Moreover, at no point does the combination of these eight references teach or suggest using an attenuated measles virus in a composition containing attenuated rubella virus to reduce the number of viable cancer cells in a mammal. The Asada reference and the Sato *et al.* reference fail to correct the deficiencies of these eight references. The Asada reference discloses treating human cancer with mumps virus, while the Sato *et al.* reference discloses an attenuated mumps virus therapy of carcinoma of the maxillary sinus. Neither of these two references, when combined with the other eight references, provides any teaching or suggestion to use an attenuated measles virus in a composition containing attenuated rubella virus to reduce the number of viable cancer cells in a mammal. In fact, the Asada and Sato *et al.* references do not mention rubella viruses, let alone attenuated rubella viruses. Thus, the combination of the ten cited references does not render claim 17 obvious.

In light of the above, Applicants respectfully request reversal of the Examiner's rejection of claim 17 under 35 U.S.C. § 103.

Issue #5: Whether the subject matter of claims 18 and 19 would have been obvious in view of the Bateman *et al.* 2000 reference combined with either the Weibel *et al.* reference or the Usonis *et al.* reference, in further view of the Duprex *et al.* reference, and further in light of the Lindarkis *et al.* abstract, the Bateman *et al.* 1999 abstract, the Taqi *et al.* reference, the Bluming *et al.* reference, and the Johnston *et al.* reference?

A. Grouping of Claims for Issue #5

Claims 18 and 19 stand or fall together.

B. Arguments for Reversal of Examiner's Rejection Regarding Issue #5

Claims 18 and 19 recite a method for reducing the number of viable cancer cells in a mammal using an attenuated measles virus genetically modified to express a marker polypeptide where expression of the marker polypeptide correlates with replication of the attenuated measles virus. The combination of cited references does not teach or suggest such a method. For the reasons explained above, the combination of (1) the Bateman *et al.* 2000 reference, (2) the Weibel *et al.* reference, (3) the Usonis *et al.* reference, (4) the Lindarkis *et al.* abstract, (5) the Bateman *et al.* 1999 abstract, (6) the Taqi *et al.* reference, (7) the Bluming *et al.* reference, and (8) the Johnston *et al.* reference does not teach or suggest reducing the number of viable cancer cells in a mammal using an attenuated measles virus. The ninth reference, the Duprex *et al.* reference, merely discloses the use of a recombinant measles virus to monitor virus spread from cell to cell. At no point does the combination of these nine references suggest that a person having ordinary skill in the art should make an attenuated measles virus genetically modified to express a marker polypeptide and use that attenuated measles virus to reduce the number of viable cancer cells in a mammal. Thus, the cited references do not render claims 18 and 19 obvious.

In light of the above, Applicants respectfully request reversal of the Examiner's rejection of claims 18 and 19 under 35 U.S.C. § 103.

Issue #6: Whether the subject matter of claim 20 would have been obvious in view of the Galanis *et al.* abstract or the Russell *et al.* abstract combined with either the Weibel *et al.* reference or the Usonis *et al.* reference, and further in light of the Lindarkis *et al.* abstract, the Bateman *et al.* 1999 abstract, the Taqi *et al.* reference, the Bluming *et al.* reference, and the Johnston *et al.* reference?

Claim 20 recites a method for reducing the number of viable melanoma cells, carcinoma cells, glioma cells, or myeloma cells in a mammal using an attenuated measles virus. The combination of cited references does not teach or suggest such a method. The Galanis *et al.* abstract discloses that glioma cell lines transfected with plasmids encoding FMGs form syncytia. The Galanis *et al.* abstract also discloses that the authors are in the process of producing adenoviruses and bicistronic retroviruses. The Russell *et al.* abstract is similar to the Galanis *et al.* abstract. In fact, the Russell *et al.* abstract discloses that glioma cell lines transfected with plasmids encoding FMGs form syncytia. The Russell *et al.* abstract also discloses that the transfected cells have suppressed tumorigenicity and that the authors are in the process of producing viral vectors. Again, being in the process of producing viral vectors such as adenoviral and retroviral vectors is unrelated to the use of an attenuated measles virus to reduce the number of viable cancer cells in a mammal. The Weibel *et al.* reference discloses vaccination results obtained from children vaccinated with a combined measles and mumps vaccine, while the Usonis et al. reference discloses vaccination results obtained from children vaccinated with a combined measles, mumps, and rubella vaccine. Neither reference discusses viral vectors, the use of viral vectors, or the use of attenuated measles virus to reduce the number of viable cancer cells in a mammal.

The Johnston *et al.* reference discloses that wild-type, lymphotropic measles viruses possess different cell tropisms than vaccine strains of measles virus. In addition, the Johnston *et al.* reference discloses using recombinant vaccine measles viruses to determine that wild-type envelope glycoproteins affect cell entry and cell-to-cell spread in adherent cell cultures. At no point does the Johnston *et al.* reference teach or suggest using an attenuated measles virus to reduce the number of viable cancer cells in a mammal.

The Linardakis *et al.* abstract discloses developing plasmid- and viral-vectors expressing FMGs under the control of inducible promoters. The Bateman *et al.* 1999 abstract discloses that the authors are constructing retroviral and adenoviral vectors for *in vivo* delivery to tumors. Clearly, developing viral vectors expressing FMGs under the control of inducible promoters and constructing retroviral and adenoviral vectors are unrelated to the use of an attenuated measles virus to reduce the number of viable cancer cells in a mammal. In addition, at no point does the Linardakis *et al.* abstract or the Bateman *et al.* 1999 abstract disclose that an attenuated measles virus would be a convenient vector to deliver measles virus DNA. The Taqi *et al.* reference is a 1981 report of the unexplained regression of Hodgkin's disease after measles infection in a 7-year-old girl. Likewise, the Bluming *et al.* reference is a 1971 report of the unexplained regression of Burkitt's lymphoma in association with measles infection. Neither of these two reports discusses viral vectors or the use of viral vectors. In fact, at no point do these two reports disclose that an attenuated measles virus would be a convenient vector to deliver measles virus DNA. It is noted that the authors of the Taqi reference proposed "a trial of attenuated live measles vaccine as in adjuvant to chemotherapy in the treatment of Hodgkin's disease in children." It is unclear from this reference what the authors are proposing. The phrase "in adjuvant to chemotherapy" is not clear. Nevertheless, proposing a trial to study the possibility of using attenuated measles vaccine in some manner falls far short of suggesting that a person having ordinary skill in the art should carry out the claimed invention. In fact, a person having ordinary skill in the art at the time Applicants filed reading the unexplained associations and the 1981 proposed trial would not have been motivated, with the required reasonable expectation of success, to use an attenuated measles virus to reduce the number of cancer cells in a mammal. Thus, taken together, it is clear that a person having ordinary skill in the art at the time Applicants filed reading the cited references would not have been motivated to administer an attenuated measles virus to a mammal to reduce the number of viable cancer cells in that mammal.

Taken together, it is clear that at no point does this combination of references suggest that a person having ordinary skill in the art should use an attenuated measles virus to reduce the number of viable melanoma cells, carcinoma cells, glioma cells, or myeloma cells in a mammal.

In light of the above, Applicants respectfully request reversal of the Examiner's rejection of claim 20 under 35 U.S.C. § 103.

The brief fee of $165 is enclosed. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: September 3, 2004

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Appendix of Claims

1. A method for reducing the number of viable cancer cells in a mammal, comprising administering attenuated measles virus to said mammal under conditions wherein the number of viable cancer cells in said mammal is reduced.

2. The method of claim 1, wherein said attenuated measles virus is administered directly to a cancer cell in said mammal.

3. The method of claim 2, wherein said cancer cell is part of a tumor.

4. The method of claim 3, wherein said attenuated measles virus is injected directly into said tumor.

5. The method of claim 4, wherein said attenuated measles virus is provided in a formulation comprising an excipient.

6. The method of claim 5, wherein said attenuated measles virus formulation is provided continuously to said mammal.

7. The method of claim 5, wherein said attenuated measles virus formulation is provided in pulses to said mammal.

9. The method of claim 1, wherein said attenuated measles virus is administered systemically to said mammal.

11. The method of claim 1, wherein said attenuated measles virus is administered at a dose greater than about 10^3 pfu.

12. The method of claim 11, wherein said dose is about 10^5 pfus.

13. The method of claim 11, wherein said dose is about 10^6 pfus.

14. The method of claim 11, wherein said dose is about 10^7 pfus.

15. The method of claim 11, wherein said dose is about 10^8 pfus.

16. The method of claim 1, wherein said attenuated measles virus is provided in a composition further comprising attenuated mumps virus and attenuated rubella virus.

17. The method of claim 1, wherein said attenuated measles virus is provided in a composition further comprising attenuated rubella virus.

18. The method of claim 1, wherein said attenuated measles virus is genetically modified to express a marker polypeptide, and wherein expression of said marker polypeptide correlates with replication of said attenuated measles virus.

19. The method of claim 18, wherein said marker polypeptide is β-galactosidase or Green Fluorescent Protein.

20. The method of claim 1, wherein said cancer cells are selected from the group consisting of melanoma cells, carcinoma cells, glioma cells, and myeloma cells.

21. The method of claim 20, wherein said cancer cells are myeloma cells.

22. The method of claim 21, wherein said myeloma cells are Non-Hodgkin's Lymphoma cells.

24. The method of claim 1, wherein said attenuated measles virus is provided within a vaccine formulation.

26. The method of claim 24, wherein said vaccine is the MMR-II vaccine.

28. The method of claim 1, wherein said attenuated virus is selected from the group consisting of the Edmonston Zagreb measles strain, the Edmonston-Enders strain, the Moraten strain, and the Moraten Berna strain.

29. The method of claim 1, wherein said attenuated virus comprises a strain obtained after serial passage of either the Moraten strain or the Moraten Berna strain on non-human cells.

30. The method of claim 1, wherein said attenuated virus comprises a strain obtained after serial passage of the Edmonston strain, the Edmonston Zagreb strain, or the Edmonston Enders strain on non-human cells.

31. The method of claim 1, wherein said attenuated virus comprises at least one point mutation in a wild-type or attenuated measles virus genome.

32. The method of claim 31, wherein said attenuated virus does not comprise contiguous point mutations.

33. The method of claim 11, wherein said dose is about 10^{12} pfu.

[CANCER RESEARCH 60, 4975–4978, September 1, 2000]

Announcements

(Requests for announcements must be received at least three months before publication.)

FUTURE ANNUAL MEETINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH

2001 March 24–28, New Orleans, LA
2002 April 6–10, San Francisco, CA
2003 April 26–30, Philadelphia, PA

2001 AACR-PEZCOLLER INTERNATIONAL AWARD FOR CANCER RESEARCH (US $75,000)

The AACR-Pezcoller International Award for Cancer Research is given annually to a scientist anywhere in the world who has made a major scientific discovery in the field of cancer, who continues to be active in the field, and whose ongoing work holds promise for future substantive contributions to cancer research. The Award recognizes extraordinary basic or translational cancer research. The Award will be presented to a single investigator for his or her highly original work. Under extraordinary circumstances, two individuals may be selected to share the Award when their investigations are clearly related and have resulted in prizeworthy work. The Awardee will be selected by an international committee of AACR members appointed by the AACR President with the agreement of the Council of the Pezcoller Foundation. The selection will be based solely on the Awardee's scientific accomplishments without regard to race, gender, nationality, geographic location, or religious or political views.

The Pezcoller Foundation was established in 1982 by Professor Alessio Pezcoller, a dedicated Italian surgeon who has made important contributions to medicine throughout his career and who, through his foresight, vision, and generous gift in support of the formation of the Foundation, stimulated others to make significant advances in cancer research. Over the past decade the Pezcoller Foundation, in collaboration with the E.S.O.—European School of Oncology, gave a major biennial award for outstanding contributions to cancer and cancer-related biomedical science.

The American Association for Cancer Research (AACR) was founded in 1907 by eleven physicians and scientists dedicated to the conquest of cancer and now has over 15,000 members in more than 60 countries who are experts in basic, clinical, and translational cancer research. The AACR is dedicated to its mission of preventing and curing cancer through the communication of important scientific results in a variety of forums including publications, meetings, and training and educational programs. Because of the commitment of the Foundation and the AACR to scientific excellence in cancer research, these organizations are now collaborating annually on the presentation of this Award. This will strengthen international collaborations and will be a catalyst for advancements in cancer research internationally.

The winner of the AACR-Pezcoller International Award for Cancer Research will give an award lecture during the AACR Annual Meeting in New Orleans, Louisiana, USA (March 24–28, 2001) and will receive the Award in a ceremony at the Foundation's headquarters in Trento, Italy, after the Annual Meeting. The Award consists of a prize of US $75,000 and a commemorative plaque.

The Foundation and the AACR are now soliciting nominations for the 2001 Award. Nominations can be made by any scientist who is now or has been affiliated with an institution engaged in cancer research. Institutions or organizations are not eligible for this award, and candidates may not nominate themselves.

There is no official application form for this award. The nomination package should consist of the following:

- the candidate's *curriculum vitae*
- an indication of the most important references in the candidate's *curriculum vitae* and list of publications
- a letter of recommendation, written in English, (500 words, maximum) describing the candidate's major scientific achievements and explaining the impact of these achievements on progress in cancer research

The deadline for nominations for this award is October 2, 2000.

Nominators are asked to maintain the confidentiality of the nomination process and to refrain from informing the candidate about the nomination.

Nominators should submit the original plus 12 copies of their nominations and supporting materials to:

AACR-Pezcoller International Award for Cancer Research
% American Association for Cancer Research, Inc.
Public Ledger Building, Suite 826
150 South Independence Mall West
Philadelphia, PA 19106-3483

Questions about the nomination process should be directed to the AACR Office via FAX at (215) 440-9313 or E-mail aacr@aacr.org.

CALL FOR NOMINATIONS FOR AACR AWARDS

The AACR presents the following awards to distinguished scientists at its Annual Meeting. The Awards Committee, consisting of different subsections, will recommend candidates for each award to the AACR Executive Committee. Following is a description of each award. Members wishing to make nominations should provide a short description of the candidate's accomplishments and the candidate's *curriculum vitae*; the subcommittee involved will obtain further documentation on suitable candidates. Nominations may be directed to the Association Office for forwarding to the appropriate subcommittee. This material should be received no later than **October 2, 2000.**

AACR-G. H. A. Clowes Memorial Award. Eli Lilly and Company established the Clowes Memorial Award Lecture in 1961 to honor Dr. G. H. A. Clowes, who was a founding member of the AACR and a research director of Eli Lilly. The purpose of the award is to give "recognition of outstanding research accomplished in some recent period." The Clowes Award should recognize outstanding recent accomplishments in basic cancer research, and the Board of Directors construes this to mean both laboratory research and epidemiological investigations.

AACR-Joseph H. Burchenal Clinical Research Award. Bristol-Myers Squibb Company has established this award to recognize outstanding achievements in clinical cancer research. It is named for Dr. Joseph H. Burchenal, past president and honorary member of the AACR, and a leading figure in the field of cancer chemotherapy. There are no restrictions on the age or geographic location of the awardee.

AACR-Richard and Hinda Rosenthal Foundation Award. The Rosenthal Foundation has established this award to "recognize research which has made or gives the promise of soon making a notable contribution to improved clinical care in the field of cancer." The Foundation wishes to honor and provide incentive to young investigators relatively early in their careers. It has, therefore, stipulated that the Association restrict the award to individuals who are engaged in the practice of medicine, who reside in the Americas, and who will not be more than 50 years of age at the time of the award (March 2001).

AACR-Cornelius P. Rhoads Memorial Award. In 1979, an anonymous donor established this award in memory of Dr. Cornelius P. Rhoads, a founder and the first Director of the Sloan-Kettering Institute for Cancer Research. This annual award is intended to give recognition to an "individual on the basis of meritorious achievement in cancer research." In accordance with the donor's wishes, the awardee must be a young investigator; therefore, the Board of Directors of the Association has stipulated that the recipient must not have reached his or her 41st birthday by the time of the award (March 2001).

AACR-Bruce F. Cain Memorial Award. The Warner-Lambert Company instituted this award to honor the memory of Dr. Bruce F. Cain of New Zealand for his work in the "design, synthesis, and biological evaluation of potential anticancer drugs." The purpose of the award is to "give recognition to an individual or research team for outstanding preclinical research that has implications for the improved care of cancer patients." Examples of such research include discovery of a significant new anticancer agent and major contributions to a compound's application as an antitumor agent. The award will recognize outstanding contributions in the fields of medicinal chemistry, biochemistry, or tumor biology as related to drug discovery; will encompass anticancer, antiviral, and antifungal agents; will have no age limit; and will be international in scope.

AACR-American Cancer Society Award for Research Excellence in Cancer Epidemiology and Prevention. The American Cancer Society sponsors this award to honor outstanding achievements in the fields of epidemiology, biomarkers, and prevention. There are no age or geographical restrictions on the awardee.

AACR-DeWitt S. Goodman Lecture. The DeWitt S. Goodman Lecture supported by contributions from two loyal members of the AACR, was established in memory of Dr. DeWitt S. Goodman, an international leader in the field of nutrition and cancer and cancer prevention. The lecture is given by a scientist who has made significant contributions to the field of cancer prevention.

AACR-Women in Cancer Research Charlotte Friend Memorial Lecture. This award is given to honor renowned virologist and discoverer of the Friend virus and Friend Cells, Dr. Charlotte Friend, for her pioneering research on viruses, cell differentiation, and cancer. This annual award is intended to "give recognition to an individual for meritorious contributions to the field of cancer research." There are no restrictions on the age or geographic location of the awardee.

APPLICATIONS NOW AVAILABLE FOR THE AACR GERTRUDE B. ELION CANCER RESEARCH AWARD

Accepting Applications from Assistant Professors throughout the World
Supported by an Educational Grant from Glaxo Wellcome Oncology

The AACR Gertrude B. Elion Cancer Research Award fosters basic, clinical, or translational research by a non-tenured, tenure-tracked scientist at the level of Assistant Professor or equivalent at an academic institution anywhere in the world. This is a one-year grant of at least $30,000 and is supported by an educational grant from Glaxo Wellcome Oncology. Travel to the AACR Annual Meeting to accept the award is also provided.

Candidates must be nominated by an Active, Corresponding, Emeritus, or Honorary Member of AACR and submit a detailed application. Applicants must be current members of the AACR or submit a complete application for membership in the Association with the Award application. Individuals holding the rank of Adjunct Professor or Instructor, tenured faculty, permanent national government employees, and employees of private industry are not eligible. **The application deadline is Friday, December 15, 2000.**

The application form and complete guidelines can be downloaded from the AACR Website: www.aacr.org. Hard copies of the application materials can also be requested by contacting: Bryan Henshaw • AACR • Public Ledger Building, Suite 826 • 150 South Independence Mall West • Philadelphia, PA 19106-3483 • Telephone: (215) 440-9300 • FAX: (215) 440-9372 • E-mail: henshaw@aacr.org.

APPLICATIONS NOW AVAILABLE FOR AACR CAREER DEVELOPMENT AWARDS

Accepting Applications from Assistant Professors throughout the World
Provided by educational grants from:
National Foundation for Cancer Research
The Susan G. Komen Breast Cancer Foundation
Additional sponsors to be announced

The AACR Career Development Awards foster cancer research by young scientists who are in the first or second year of a full-time, tenure-track faculty appointment at the level of Assistant Professor or equivalent at an academic institution anywhere in the world.

The AACR Career Development Awards are two-year grants that provide $50,000 per annum. AACR Career Development Awards are intended to cover direct research expenses, which may include payments to research assistants. These awards are not intended to underwrite or supplement the salary of the awardee. Candidates must be nominated by an Active, Corresponding, Emeritus, or Honorary Member of AACR and submit a detailed application. Applicants must be current members of the AACR or submit a complete application for membership in the Association with the Awards application. Individuals holding the rank of Adjunct Professor or Instructor, tenured faculty, permanent national government employees, and employees of private industry are not eligible. **The application deadline is Friday, December 15, 2000.**

The application form and complete guidelines can be downloaded from the AACR Website: www.aacr.org. Hard copies of the application materials can also be requested by contacting: Bryan Henshaw • AACR • Public Ledger Building, Suite 826 • 150 South Independence Mall West • Philadelphia, PA 19106-3483 • Telephone: (215) 440-9300 • FAX: (215) 440-9372 • E-mail: henshaw@aacr.org.

APPLICATIONS NOW AVAILABLE FOR AACR RESEARCH FELLOWSHIPS

For Postdoctoral and Clinical Research Fellows throughout the World

The AACR Research Fellowships in basic, clinical, prevention, and translational research foster cancer research by young scientists currently at the postdoctoral or clinical research fellow level. AACR Fellowships provide a one- or two-year grant of $30,000 per annum plus travel to the AACR Annual Meeting. AACR Research Fellowships are generously sponsored by organizations including: American Association for Cancer Research, Amgen, Inc., Bristol-Myers Squibb Oncology, Cancer Research Foundation of America, and Sidney Kimmel Foundation for Cancer Research. (See AACR Website for complete list of sponsors and Fellowships.)

Candidates must be nominated by an Active, Corresponding, Emeritus, or Honorary Member of AACR and submit a detailed application. Applicants must be current members of the AACR or submit a complete application for membership in the Association with the Fellowships application. Fellowships candidates must have been fellows for at least two years but not more than five years prior to the beginning of the award year (July 2001). Academic faculty holding the rank of Adjunct Professor, Associate Professor, Assistant Professor, or higher, graduate or medical students, medical residents, permanent national government employees, and employees of private industry are not eligible. **The application deadline is Friday, December 15, 2000.**

The application form and complete guidelines can be downloaded from the AACR Website: www.aacr.org. Hard copies of these materials can also be requested by contacting: Bryan Henshaw • AACR • Public Ledger Building, Suite 826 • 150 South Independence Mall West • Philadelphia, PA 19106-3483 • Telephone: (215) 440-9300 • FAX: (215) 440-9372 • E-mail: henshaw@aacr.org.

AACR SPECIAL CONFERENCES IN CANCER RESEARCH

A number of meetings are now being organized in the AACR's series of smaller scientific meetings. Following are the topics, dates, locations, and program committees for these meetings. When full details of each meeting are available, AACR members will be the first to receive complete brochures and application forms for participation in these important conferences. Nonmembers may receive this information by sending their names and addresses to Meetings Mailing List, American Association for Cancer Research, Public Ledger Building, 150 South Independence Mall West, Suite 826, Philadelphia, PA 19106-3483. Up-to-date program information is also available via the Internet at the AACR's website (http://www.aacr.org/confmc.html).

CYTOKINES AND CANCER: REGULATION, ANGIOGENESIS, AND CLINICAL APPLICATIONS

September 20–24, 2000
Vail Cascade Hotel & Club, Vail, CO

Chairpersons
Janice P. Dutcher, Bronx, NY
Michael Lotze, Pittsburgh, PA
Giorgio Trinchieri, Dardilly, France

ANGIOGENESIS AND CANCER: FROM BASIC MECHANISMS TO THERAPEUTIC APPLICATIONS

October 11–15, 2000
Grand Traverse Resort, Traverse City, MI

Chairpersons
Judah Folkman, Boston, MA
David A. Cheresh, La Jolla, CA

NEW TARGETS FOR CANCER INTERVENTION

(Joint Conference with the Israel Cancer Association)
November 12–15, 2000
Royal Beach Hotel, Eliat, Israel

Chairpersons
Webster K. Cavenee, La Jolla, CA
Pnina Fishman, Petah Tikva, Israel

MOUSE MODELS OF CANCER

November 29–December 3, 2000
Hyatt Regency La Jolla, La Jolla, CA

Chairpersons
Tyler Jacks, Cambridge, MA
Ronald A. DePinho, Boston, MA

MOLECULAR BIOLOGY AND
NEW THERAPEUTIC STRATEGIES:
CANCER RESEARCH IN THE 21ST CENTURY
(5th Joint Conference with the Japanese Cancer Association)
February 12–16, 2001
Maui Marriott Resort, Maui, HI

Chairpersons

Webster K. Cavenee, La Jolla, CA
Setsuo Hirohashi, Tokyo, Japan

CANCER SUSCEPTIBILITY GENES AND
MOLECULAR CARCINOGENESIS
February 25–March 1, 2001
Hyatt Regency Lake Tahoe, Incline Village, NV

Chairpersons

Allen Balmain, San Francisco, CA
Bruce A.J. Ponder, Cambridge, England

CALENDAR OF EVENTS

Novel Molecular Targets for Cancer Therapy, October 5–6, 2000, Buenos Aires, Argentina. Sponsored by: National Cancer Institute, National Institutes for Dental and Craniofacial Disorders, and Sbarro Cancer Center. Keynote Speaker: Bruce Chabner, Massachusetts General Hospital; Chairperson: Adrian Senderowicz; Co-Chairperson: Antonio Giordano. Contact Secretariat, phone: 54.11.4792.7067; fax: 54.11.4792.1218; e-mail: bacancermeeting@yahoo.com.

Frontiers of Cellular Microbiology and Cell Biology: EuroConference on Signaling and Cytoskeleton Plasticity, October 7–12, 2000, Giens, France. Contact: Dr. J. Hendekovic, European Science Foundation, 1 quai Lezay-Marnesia, 67080 Strasbourg Cedex, France. Phone: 33.388.76.71.33; Fax: 33.388.36.69.87; E-mail: euresco@esf.org: Website: http://www.esf.org.euresco.

Eighth Conference on Radioimmunodetection and Radioimmunotherapy of Cancer, October 12–14, 2000, Princeton, NJ. Abstract Deadline: May 1, 2000. Contact: Lois Gillespie, Garden State Cancer Center, 520 Belleville Ave., Belleville, NJ 07109. Fax: 973-844-7020; E-mail: *gscancer@att.net.*

Cancer Therapy for the New Millennium. October 12–14, 2000, Palermo, Italy. Contact: Center for Bio-Medical Communication, Inc., 433 Hackensack, NJ 07601. Phone: (201) 342-5300; Fax: (201) 342-7555; E-mail: cmeinfo@cbcbiomed.com; Website: www.cbcbiomed.com.

20th Annual Nurses Cancer Symposium, October 16–18, 2000, La Jolla Marriott, La Jolla, CA. Contact: Ruthanne Crawford, Stevens Cancer Center, 9888 Genesee Avenue, La Jolla, CA 92037. Phone: 858.626.6794; Fax: 858.626.6793; E-mail: crawford.ruthanne@scrippshealth.org.

2nd International Conference on Tumor Microenvironment, Progression, Therapy & Prevention, October 29–November 1, 2000, Tiberias, Israel. Contact: The Secretariat, 2nd International Conference on Tumor Microenvironment, Progression, Therapy & Prevention, P.O. Box 50006, Tel Aviv, Israel. Phone: 972.3.514000; Fax: 972.3.5140077; E-mail: tumormicro@kenes.com.

Hong Kong Academy of Medicine Second International Congress, November 2–5, 2000, Hong Kong Academy of Medicine, Hong Kong. Contact: Congress Secretariat, 10/F, Hong Kong Academy of Medicine Jockey Club Building, 99 Wong Chuk Hang Road, Aberdeen, Hong Kong. Phone: (852) 2871 8787; Fax: (852) 2871 8989.

First International Symposium on Translational Research in Breast and Ovarian Cancers, November 3–5, 2000, Four Seasons Hotel Dublin, Dublin, Ireland. Contact: Kim Pearson, The CBCE/S.G. Madison, Dallas, TX. Phone: 972.929.1900 x 104; Fax: 972.929.1901; E-mail: kimp@sgmadison.com.

ONS Institutes of Learning, November 3–5, 2000, Charlotte Convention Center, Charlotte, NC. Contact: Oncology Nursing Society, 501 Holiday Drive, Pittsburgh, PA 15220-2749. Phone: 412.921.7373; Fax: 412.921.6565; E-mail: customer.service@ons.org.

World Assembly on Tobacco Counters Health (WATCH 2000), December 4–8, 2000, India. Website: http://www.watch-2000.org.

Seventh Hong Kong International Cancer Congress, December 7–9, 2000, Hong Kong Academy of Medicine, Hong Kong. Contact: 7th HKICC Congress Secretariat, Department of Surgery, University of Hong Kong Medical Centre, Queen Mary Hospital, Hong Kong. Phone: (852) 2818-0232 / (852) 2855-4235; Fax: (852) 2818-1186; E-mail: mededcon@hku.hk.

6th National Conference on Oncology Nursing Research, February 8–10, 2001, Ponte Vedra Beach, FL. Call for Abstracts deadline: August 21, 2000; call for New Investigator Award Application deadline: September 15, 2000; call for ONS/ACS State-of-the-Science Lecture Abstract Deadline: August 21, 2000. E-mail: research@ons.org. Website: www.ons.org.

4th International Symposium on Leukemia and Lymphoma, March 7–10, 2001, Amsterdam, The Netherlands. Contact: VU Conference Service, DeBoelelaan 1105, NL-1081 HV Amsterdam, The Netherlands. Phone: 31.20.444.5790; Fax: 31.20.444.5825; E-mail: vu_conference@dienst.vu.nl.

International Conference on Radiation Protection of Patients: Diagnostic and Interventional Radiology, Nuclear Medicine, and Radiotherapy, March 26–30, 2000, Convention and Exhibition Centre of Torremolinos, Malaga, Spain. Registration deadline: November 1, 2000. Website: http://www.pruma.uma.es/ci2001.htmlx.

The Eighth International Conference on Human Antibodies & Hybridomas, April 23–25, 2001, Radisson SAS Hotel, Praque, Czech Republic. Deadline for abstract submissions: November 17, 2000. Contact: John Herriot, HAH 2001, Meetings Management, The Barn, Rake Meadow, Station Lane, Milford, Surrey, GU8 5AD, United Kingdom. Phone: 44.1483.427770; Fax: 44.14834.428516; E-mail: jherriot@meetingsmgmt.u.net.com; Website: www.meetingsmanagement.com.

Glioma: from Gene to Cure, April 26–28, 2001, Amsterdam, The Netherlands. Contact: European Cancer Centre, P.O. Box 9236, NL-1006 AE Amsterdam, The Netherlands. Phone: 31.0.20.346.2547; Fax: 31.0.20.346.2525; E-mail: ecc@ikca.nl; Website: http://www.EurCanCen.org.

4th International Gastric Cancer Congress sponsored by The International Gastric Cancer Association and Memorial Sloan Kettering Cancer Center, April 30–May 2, 2001, New York Hilton, New York, N.Y. Contact: Jan Sharkey at (e-mail) jsharkey@slackinc.com or (website) www.mskcc.org/igcc2001.

UK Radiological Congress 2001 (UKRC 2001), May 21–23, 2001, Wembley Conference & Exhibition Centre, London, UK. Call for papers deadline: November 20, 2000. Contact: UKRC Secretariat, PO Box 2895, London, W1A 5RS, UK. Phone: 44.0.20.7307.1410/20; Fax: 44.0.20.7307.1414; E-mail: ukrc@dial.pipex.com; Website: ukrc.org.uk.

9th Asian Pacific Congress of Clinical Biochemistry, November 11–16, 2001, Ashok Hotel, New Delhi, India. Fax: 91.11.6011543; E-mail: cms@de13.vsnl.net.in.

Correction

It has come to our attention that the data shown in Figure 3 of our manuscript (A. Bateman *et al.*, Cancer Res. *60:* 1492–1497, 2000) are derived from a slightly different experimental protocol than those described in the following text from page 1496 (lines 28–35):

Established Tumors Can Be Eradicated by Transduction with Plasmid DNA Encoding FMG cDNA. Human tumor xenografts of HT1080 or Mel624 cells were injected s.c. into nude athymic mice at a dose of 10^6 tumor cells/mouse. At this dose, 90–100% of mice develop small, palpable tumors by 72 h after tumor cell seeding. Tumors were transfected with 10 μg of plasmid DNA complexed with Efectene lipid (Qiagen). The subsequent development of tumor growth was then measured with time as shown in Fig. 3.

The protocol should read as follows:

Tumorigenicity Can Be Abrogated by Pretransduction with Plasmid DNA Encoding FMG cDNA. Tumor cells were transfected with 10 μg of plasmid DNA complexed with Efectene lipid (Qiagen). Twenty-four h later, transduced human tumor xenografts of HT1080 or Mel624 cells were injected s.c. into nude athymic mice at a dose of 10^6 tumor cells/mouse. At this dose, 90–100% of control mice develop small, palpable tumors by 72 h after tumor cell seeding. The subsequent development of tumor growth was then measured with time as shown in Fig. 3.

All other data reported in the manuscript have been thoroughly checked and are correct as described.

Andrew Bateman
Francis Bullough
Stephen Murphy
Lisa Emiliusen
Dimitri Lavillette
François-Loic Cosset
Roberto Cattaneo
Stephen J. Russell
Richard G. Vile